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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/822,033	03/24/1997	WAYNE A. MARASCO	43471-FWC	5884

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/822,033	MARASCO ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/22/1994* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a file wrapper continuation of 08/199, 070, filed February 22, 1994.

Applicants' amendment filed September 15, 2004 has been received and entered. No claims have been amended. Claims 1, 3-16 are pending and currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 7-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Beug *et al.*, Chaudhary *et al.* and Wu *et al.* for the reasons below and as set forth in the previous office action.

Applicants summarize the teachings of both Beug *et al.* and Wu *et al.* noting that each teach a fusion protein that is made by chemical conjugation of a targeting protein and polycation, not a recombinantly made protein (middle of page 5). Applicants argue that while Chaudhary

et al. teach a fusion protein, it is used to deliver a protein, not a nucleic acid as required by the instant claims. Further, there is no specific teaching nor motivation to use the teachings of Chaudhary *et al.* with that of Beug *et al.* and Wu *et al.*, therefore the use of fusion proteins for the targeted delivery of nucleic acids was not known at the time of filing (bottom of page 5, and 7-8). Giving the cited references, Applicants argue that Examiner's statement that the use of fusion proteins to delivery a polynucleotide is inaccurate (page 5). Noting the previously filed declaration of Dr. Wayne Marasco, a co-inventor and co-author on the Li *et al.* reference, Applicants argue that the use of recombinant fusion proteins provided surprising advantages over chemical conjugates (page 6). More specifically, Applicants argue that the data in the Li *et al.* reference provides clear evidence that the use of the ErbB2 antibody-protamine fusion protein provided a greater specificity than that of the chemical conjugate, pointing to figures 6C and 7B in the post-filing reference of Li *et al.* where an 8 to 10 fold increase higher expression in cells which express the ErbB2 cell surface receptor versus cells which do not express ErbB2 receptor is obtained using the fusion protein (page 6). Moreover, it is argued that one would expect that this approach would extend to other fusion proteins (top of page 7). See Applicants' amendment, pages 5-8. Applicants' arguments have been fully considered, but not found persuasive.

Initially, Examiner would agree that a recombinantly made fusion protein used to deliver a polynucleotide was not known in the art at the time of filing (as presently claimed), however Examiner's statement that the use of fusion proteins is not inaccurate because it was made in the context encompassing a fusion protein made by any means. More specifically, the teachings of Wu *et al.* provide evidence that a targeting molecule was fused, albeit chemically, to nucleotide binding agents such as polylysine, polyarginine, polyornithine, as well as other DNA binding

protein known in the art such as hisotones, avidin, and protamines (page 7, bottom of the page). Here, Wu *et al.* clearly teach the combination of a cell targeting protein with a nucleotide binding molecule as one fusion protein. Because Wu *et al.* does not teach a chemical linkage that would result in the same fusion protein as one made recombinantly, the reference can not be used as anticipatory reference in a 102 type rejection. However, it does provide clear evidence that fusion proteins comprising the two protein elements recited in claim 1(a) were made and used to deliver polynucleotides (claim 1(b) limitation) at the time of filing. Thus, it is maintained that at the time of filing the use of fusion proteins for the delivery of polynucleotides was known.

Applicants do not contest that the cited references teach the limitations that anticipate the embodiments encompassed by the claims nor that there would be a reasonable expectation of success as required in making a *prima facie* case under 35 USC 103. The issue that remains is whether the combined references provide adequate motivation to combine to make obvious the claimed product. As noted in the previous office actions, the instant specification teaches that the methodology used to generate a fusion protein is that known and conventional in the art at the time of filing. Again, the teachings in the present specification that a recombinantly produced protein is one which produced as one contiguous protein using conventional and standard molecular techniques known in the art (for example page 24, starting at third full paragraph). In the basis of the rejection Chaudhary *et al.* was cited to substantiate the statements in the instant specification regarding the technology of making recombinant fusion proteins. Further, Chaudhary *et al.* provides teaching for specific embodiments in the claims and a clear expectation of success for the use of recombinant technology in making fusion proteins. Examiner would agree that Chaudhary *et al.* does not teach nor provide the specific motivation to

deliver a polynucleotide in the teachings, however as discussed above this is not why Chaudhary *et al.* is cited. The specific motivation to combine the teachings of the cited refrences comes from Beug *et al.* who teach fusion proteins for the delivery of polynucleotides, and that any method could be used to generate the fusion protein and specifically suggest recombinant technology. Similar to Wu *et al.* Beug *et al.* teach that when the peptides are coupled, for example a ligand to polylysine, and importantly that recombinant methods can be used to generate the recombinant protein (see for example page 7). Applicants' arguments that the combined references provide only for chemical linkage, is not persuasive because fusion proteins comprising two protein portions, one comprising a targeting moiety and one that binds a polynucleotide, were known in the art at the time of filing, and the cited references give specific suggestion to use methods known in the art such as generating them recombinantly.

Finally, regarding Applicants arguments that the declaration of Dr. Wayne Marasco, and evidence provided in the post-filing reference of Li *et al.*, demonstrates that the use of recombinant fusion proteins provided surprising advantages over chemical conjugates, in particular it is argued that the ErbB2 antibody-protamine fusion protein provided a greater specificity than that of the chemical conjugate, pointing to figures in the post-filing. In addition, it is argued that one would expect that this approach would extend to other fusion proteins. Upon examination of the experiments represented by the two figures referred to by Applicants, it is found that Applicants conclusion of surprising results can not be made. Initially, an analysis for the comparison of the two figures does not provide a comparison of recombinantly made and chemically linked fusion proteins. Figure 7 is simply a test of the affect on how the order of mixing the particular agents in the composition affect transfection. Moreover, a direct

comparison can not be made because while the end point of luciferase activity was measured, the amounts of materials used and length of time before measuring luciferase activity are different. the experiments, each being critical in the final amount of gene delivered and expressed. In addition, a comparison of other fusion proteins indicates that the result relied upon in Applicants arguments is variable and dependent on the composition (compare for example ScFv-P-S and ScFv-P-L). Therefore, in light of the fact that figure 7 does not represent a chemically linked fusion protein and that the experiments of figure 6 and 7 were performed under different conditions, it is found that one can not draw any comparative conclusions that support an unexpected property of the claimed product over that in the prior art. It is noted that the present specification does not provide any evidence nor discussion for an unexpected property of the claimed invention. A complete reading of the Li *et al.* reference indicates that other problems of recombinantly made fusion proteins also exist and was the reason for pursuing the compositions tested in figure 7(for example page 536). Even if one were to accept that a specific product had an unexpected property, based on the teachings of Li *et al.* as a whole for the problems of isolating the fusion protein and variability in different constructs, it is not apparent that the skilled artisan would agree with Applicants assertion that the approach would extend to other fusion proteins. Consistent with the rule that all evidence of nonobviousness must be considered when assessing patentability, the PTO must consider comparative data in the specification in determining whether the claimed invention provides unexpected results. *In re Margolis*, 785 F.2d 1029, 1031, 228 USPQ 940, 941-42 (Fed. Cir. 1986). However, " [i]t is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice." *In re De Blauwe* , 736 F.2d 699,

705, 222 USPQ 191, 196 (Fed. Cir. 1984); see also *In re Wood* , 582 F.2d 638, 642, 199 USPQ 137, 140 (CCPA 1978) ("Mere lawyer's arguments and conclusory statements in the specification, unsupported by objective evidence, are insufficient to establish unexpected results."); *In re Lindner* , 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972) (" [M]ere conclusory statements in the specification . . . are entitled to little weight when the Patent Office questions the efficacy of those statements.").

The claims broadly encompass any combination of targeting molecule and nucleic acid binding moiety. While the ScFv-P-S may display an 8-10 fold more luciferase activity to cells with than without ErbB2 (page 564 of Li *et al.*), clearly other constructs such as the ScFv-P-L which shows half the luciferase activity in ErbB2 expressing cells and greater non-specific activity (figure 6(c)) do not. In summary, at the time of filing Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching for all the embodiments encompassed by the instant claims, and the specific motivation to generate a recombinant targeting protein complex. In particular, where two protein components are provided, such as an antibody coupled to a second protein moiety, there is specific motivation to make this fusion protein recombinantly for the reasons set forth by Wu *et al.* and Chaudhary *et al.* Further, the use of a targeting antibody would generally be accepted to provide a more selective targeting, and as evidenced by Chaudhary *et al.* and Wu *et al.* the selection can be very great. Applicants arguments and reliance on unexpected properties of the claimed products are not found persuasive found nor convincing based on the evidence of record. Therefore, for the reasons above and of record, the rejection is maintained.

Claim 6 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Beug *et al.*, Chaudhary *et al.* and Wu *et al.* as applied to claims 1, 3-5, 7-16 above, and in further view of Ryder *et al.* for the reasons below and as set forth in the previous office action.

Applicants argue that the teaching of Ryder *et al.* does not overcome the essential deficiency of Beug *et al.*, Chaudhary *et al.* and Wu *et al.* as discussed for claims 1, 3-5, 7-16. See Applicants' amendment, page 8. Applicants' arguments have been fully considered, but not found persuasive.

As reasoned above, Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching and motivation to make obvious claims 1, 3-5, 7-16. Beug *et al.* and Wu *et al.* teach that any variety of polynucleotide binding sequences can be used in forming the complexes and and attached to the targeting moiety, however specific polynucleotide sequences are not taught. Ryder *et al.* is relied upon to teach that at the time of filing among the various species of sequences recited in claim 6, the Jun DNA binding sequences were known. As noted in the previous office action, Ryder *et al.* is not relied upon to correct deficiencies of Beug *et al.*, Chaudhary *et al.* and Wu *et al.*, rather the teachings are relied upon to teach what was known in the art at the time of filing. Ryder *et al.* provide a detailed teaching for the specific DNA binding sequences and demonstrate that they are effective in binding target DNA as evidenced by the gel shift assay (see results in figure). Applicants' arguments are unpersuasive because Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching to make obvious claims 1, 3-5, 7-16, and claim 6 is obvious in light of the teaching of Ryder *et al.* for the specific c-jun DNA binding sequences.

Therefore, for the reasons above and of record, the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach